General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C9* and *HLA-B* genotypes and phenytoin dosing.

Bibliographic Source(s)

Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014 Nov;96(5):542-8. [36 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Human Leukocyte Antigen (*HLA*)-*B*

Clinical genotyping test results for *HLA-B*15:02* are interpreted as "positive" if one or two copies of *HLA-B*15:02* are present or as "negative" if no copies of *HLA-B*15:02* are present. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in Table 1 below. The allele frequencies of *HLA-B* vary greatly among populations. Specifically, *HLA-B*15:02* is most prevalent in Oceania and in East Asian and South/Central Asian populations, ranging from 1% to more than 10%. It is less frequent in European populations (0%–1%) and apparently absent in several African populations (Supplementary Tables S3 and S4 online [see the "Availability of Companion Documents" field]). The global average derived from more than 46,000 individuals is 1.37%.

Cytochrome P450 (CYP)2C9 (*CYP2C9*)

Most clinical laboratories reporting *CYP2C9* genotype use the star allele nomenclature and may interpret the patient's predicted metabolizer phenotype (see Table 1 below and Supplementary Table S1 online [see the "Availability of Companion Documents" field]). The combination of alleles is used to determine a patient's diplotype. Not all *CYP2C9* allelic variants may be tested, influencing the accuracy of the genotype-based dose prediction, primarily in individuals of Asian or African ancestry who carry other common functionally decreased function *CYP2C9* variant alleles (Supplementary Table S5 online [see the "Availability of Companion Documents" field]). The frequencies of the *CYP2C9*2* and *3* alleles

and diplotypes derived from these and other alleles differ among racial/ethnic groups (Supplementary Tables S5–S7 online [see the "Availability of Companion Documents" field]). *CYP2C9* alleles are typically characterized as wild-type (normal function) or decreased-function alleles depending on the reported activity of the enzyme that they encode.

Table 1: Assignment of Likely Phenotype Based on Genotypes

Assignment of Likely CYP2C9 Phenotype Based on Genotype		
Likely Phenotype[a]	Genotype	Examples of Diplotypes
Extensive metabolizer (normal activity) (constitutes ~91% of patients)	An individual carrying two normal-function alleles	**1/*1*
Intermediate metabolizer (heterozygote or intermediate activity) (constitutes ~8% of patients)[c]	An individual carrying one normal-function allele plus one decreased-function allele	**1/*3, *1/*2*
Poor metabolizer (homozygous variant, low or deficient activity) (constitutes ~1% of patients)	An individual carrying two decreased-function alleles	**2/*2, *3/*3, *2/*3*
Assignment of Likely HLA-B Phenotype Based on Genotype		
Likely Phenotype[b]	Genotype	Examples of Diplotypes
Homozygous for an allele other than **15:02*; at "normal" or reduced risk of phenytoin associated cutaneous adverse reactions (constitutes ~98.6% of patients)	*HLA-B*15:02* noncarrier. No **15:02* alleles reported, often reported as "negative" on a genotyping test	**X/*X*[d]
Heterozygote or homozygous variant; at significantly increased risk of phenytoin associated cutaneous adverse reactions (constitutes ~1.4% of patients)	*HLA-B*15:02* carrier. One or two **15:02* alleles, often reported as "positive" on a genotyping test	**15:02/*X*[d], **15:02/*15:02*

CYP, cytochrome P450.

[a,b]Global frequencies presented in parentheses. Haplotype frequencies vary among populations; please see details for individual population frequencies in [a]Supplementary Tables S5–S7 online for *CYP2C9*2* and **3*, and [b]Supplementary Tables S3 and S4 online for *HLA-B*15:02* (see the "Availability of Companion Documents" field).

[c]The enzyme activity in this grouping varies widely. See Supplementary Table S2 online for activity ranges (see the "Availability of Companion Documents" field).

[d]Where *X = any genotype other than **15:02*.

Table 2: Recommended Dosing of Phenytoin/Fosphenytoin Based on *HLA-B*15:02* and *CYP2C9* Phenotype/Genotype

	*HLA-B*15:02* Carrier			*HLA-B*15:02* Noncarrier		
Phenotype/Genotype	Implication	Therapeutic Recommendation	Classification of Recommendation[a]	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2C9 extensive metabolizer	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin naive,[a] do not use phenytoin/fosphenytoin[b]	Strong	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dose.[c]	Strong
CYP2C9 intermediate metabolizer	Increased risk of phenytoin-induced	If patient is phenytoin naive,[a] do not use phenytoin/fosphenytoin[b]	Strong	Reduced phenytoin metabolism. Higher plasma	Consider 25% reduction of recommended starting	Moderate

	SJS/TEN *HLA-B*15:02* Carrier			*HLA-B*15:02* Noncarrier		
Phenotype/Genotype	Implication	Therapeutic Recommendation	Classification of Recommendation[a]	Implication	Therapeutic Recommendation	Classification of Recommendation
				concentrations will increase probability of toxicities.	maintenance dose.[c] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.	
CYP2C9 poor metabolizer	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin naive,[a] do not use phenytoin/fosphenytoin[b]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities.	Consider 50% reduction of recommended starting maintenance dose.[c] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.	Strong

CYP, cytochrome P450; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

[a]If the patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known.

[b]Carbamazepine should not be used as an alternative. Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin (see Supplementary Material online for details; see the "Availability of Companion Documents" field).

[c]Recommended maintenance dose based on patient's clinical characteristics.

Therapeutic Recommendations

*HLA-B*15:02* Recommendations

The Food and Drug Administration warning for phenytoin states, "Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*15:02*" due to the increased risk of SJS/TEN (Steven-Johnson syndrome/toxic epidermal necrolysis) in patients of Asian ancestry. The evidence linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in individuals of Asian ancestry because the frequency of *HLA-B*15:02* is very low in other populations (see Supplementary Tables S3 and S4 online for frequency information [see the "Availability of Companion Documents" field]) that have been studied. However, *HLA-B*15:02* may also occur in other populations throughout the world yet to be studied, and patients may be unaware of or fail to disclose more distant Asian ancestry in their families. Furthermore, much of the evidence (summarized in Supplementary Table S8 online [see the "Availability of Companion Documents" field]) linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in both children and adults. Therefore, regardless of the *CYP2C9* genotype and the individual's ancestry or age, if the *HLA-B*15:02* test result is positive, the recommendation is to consider using an anticonvulsant other than carbamazepine and phenytoin, unless the benefits of treating the underlying disease clearly outweigh the risks (see Table 2 above). Some evidence exists linking SJS/TEN with the *HLA-B*15:02* allele in association with the use of alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine, and thus caution should be used in choosing alternatives to phenytoin (see Supplementary Material online for details [see the "Availability of Companion Documents" field]).

CYP2C9 Recommendations

Phenytoin and fosphenytoin dose should first be adjusted according to a patient's clinical characteristics. Table 2 above summarizes the gene-based dosing recommendations for phenytoin based on CYP2C9 phenotype. The recommended phenytoin maintenance dose does not need adjustment based on genotype for CYP2C9 extensive metabolizers. Available evidence does not clearly indicate the amount of dose reduction needed to prevent phenytoin-related toxicities in CYP2C9 intermediate and poor metabolizers; thus, the recommendations should be considered conservative estimates, given the variability surrounding phenytoin dosing in an individual. On the basis of the doses reported in the pharmacokinetic and pharmacogenetic studies mentioned in the original guideline document and in Supplementary Table S9 online (see the "Availability of Companion Documents" field), at least a 25% reduction of the recommended starting maintenance dose may be considered for CYP2C9 intermediate metabolizers, with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response. For CYP2C9 poor metabolizers, consider at least a 50% reduction of starting maintenance dose, with subsequent maintenance doses adjusted based on therapeutic drug monitoring or response.

Furthermore, although *in vitro* data suggest that the degree of reduction of catalytic activity is greater for the *CYP2C9*3* variant than for the *CYP2C9*2* variant, clinical pharmacokinetic studies indicate similar dose reductions and pharmacokinetic parameters (e.g., trough levels, and serum 5-(4′-hydroxyphenyl)-5-phenylhydantoin/phenytoin ratio) for these variants as compared with the wild-type alleles. Therefore, the recommendation is to start with at least the above-recommended reduction of the maintenance dose, followed by an adjustment of dose based on therapeutic drug monitoring.

Pediatrics

Special consideration should be given to the pediatric population. Phenytoin is used in the treatment of neonatal seizures and, subsequently, after discharge from the neonatal intensive care unit. Maintaining therapeutic levels can be particularly problematic in this population. This may be due to the developmental expression of hepatic CYP2C. CYP expression and functional activities have been shown to develop at different rates within subfamilies. It has been found that activity levels of CYP2C9 are at 1% to 2% of adult values in the fetus during the first trimester. These levels gradually increase to 30% of adult values at term. There is a high variability in these levels during the first 5 months of life, with levels eventually approaching adult values somewhere between 5 months and 2 years of age. Other considerations include the fact that clearance of phenytoin is twice that of adult values in children younger than 6 years of age. This is attributed to the finding that the maximal rate of phenytoin metabolism is inversely related to age. However, this varies significantly within age subgroups. For these reasons, phenytoin therapeutic recommendations based on *CYP2C9* genotype in this population are difficult. There is only one published report describing a 2-year-old patient (*CYP2C9*2/*2* and *CYP2C19*1/*4*) presenting with phenytoin toxicity 2 h after a 15-mg/kg phenytoin loading dose with symptoms lasting 122 h. The half-life was much higher than expected (112 h vs 46.7 h), which could be explained by the influence of *CYP2C9* and *CYP2C19* genetic polymorphisms (other predisposing factors such as malnourishment, renal failure, hepatic dysfunction, and inhibition of phenytoin metabolism by other drugs were ruled out). Therefore, for pediatric patients who are CYP2C9 intermediate or poor metabolizers, dose adjustment is recommended with close therapeutic drug monitoring.

*HLA-B*15:02* and *CYP2C9* Dosing Recommendation

If both *HLAB*15:02* and *CYP2C9* genotypes are known, consider the *HLAB*15:02* genotype first, then the *CYP2C9* genotype (see Figure 1 in the original guideline document and Table 2 above).

Recommendations for Incidental Findings

Several drugs structurally and therapeutically similar to phenytoin, such as oxcarbazepine and carbamazepine, have also been associated with SJS/TEN and *HLA-B*15:02* in Asian populations (see Supplementary Material online [see the "Availability of Companion Documents" field]). The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *HLA-B* genotype and carbamazepine dosing and may have implications for choosing alternatives to phenytoin in those who carry the *HLA-B*15:02* allele. Case reports have identified cross-reactions to lamotrigine and other antiepileptic drugs in the presence of *HLA-B*15:02* (see Supplementary Material online for further discussion [see the "Availability of Companion Documents" field]). However, larger studies appear to be needed for confirmation.

CYP2C9 metabolism includes substrates from several drug classes, including nonsteroidal anti-inflammatory drugs, oral hypoglycemics/sulfonylureas, and a miscellaneous group of drugs. Reports support that patients with enhanced sensitivity to warfarin are likely to have a decreased capacity to metabolize phenytoin.

Definitions

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

An algorithm titled "Suggested Clinical Actions Based on *HLA-B*15:02* and *CYP2C9* Genotypes" is provided in the original guideline document.

In addition, the following algorithms (see the "Availability of Companion Documents" field) are provided in the supplementary online material:

- *HLA-B*15:02* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR
- *CYP2C9* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR
- *HLA-B*15:02* Genotype and Phenytoin: Point of Care Clinical Decision Support
- *CYP2C9* Genotype and Phenytoin: Point of Care Clinical Decision Support
- *HLA-B*15:02* and *CYP2C9* Genotype and Phenytoin: Point of Care Clinical Decision Support

Scope

Disease/Condition(s)

Focal and generalized convulsive status epilepticus

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Medical Genetics

Neurology

Pediatrics

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information for the interpretation of *human leukocyte antigen (HLA)-B* and/or cytochrome P450 (CYP)2C9 (*CYP2C9*) genotype

tests so that the results can guide dosing and/or use of phenytoin

Target Population

Adults and children with focal or generalized convulsive status epilepticus who are prescribed phenytoin

Interventions and Practices Considered

Dosing of phenytoin/fosphenytoin based on *human leukocyte antigen (HLA)-B*15:02* and cytochrome P450 (CYP)2C9 (*CYP2C9*) phenotype/genotype

Note: Detailed guidelines for the use of phenytoin are out of scope for this guideline.

Major Outcomes Considered

- Correct interpretation of *human leukocyte antigen (HLA)-B* and/or cytochrome P450 (CYP)2C9 (*CYP2C9*) genotype tests
- Appropriate dosing and/or use of phenytoin based on *HLA-B* and/or *CYP2C9* genotype
- Occurrences of Stevens–Johnson syndrome and toxic epidermal necrolysis based *HLA-B* and/or *CYP2C9* genotype

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The authors searched the PubMed database (1966 to April 2014 and Ovid MEDLINE (1950 to April 2014) for the keywords ([HLA OR HLA-B OR *HLA-B*15:02*] AND [phenytoin OR fosphenytoin]) and ([CYP2C9 OR cytochrome P450-2C9] AND [phenytoin OR fosphenytoin]) or [pharmacogenetics OR polymorphism] AND [phenytoin OR fosphenytoin]. A more general search was also conducted using the search terms ([phenytoin hypersensitivity] OR [phenytoin Stevens-Johnson]). Using the specified search criteria, 5,193 publications were identified. Inclusion criteria included English language publications discussing in vivo clinical outcome (e.g., Stevens-Johnson Syndrome and toxic epidermal necrolysis or phenytoin related adverse drug reactions) for phenytoin in individuals who vary by CYP2C9 and HLA-B genotype/phenotype and *in vivo* or *in vitro* pharmacokinetic data (e.g., dose-adjusted trough concentrations, clearance) for phenytoin in individuals who vary by CYP2C9 genotype/phenotype, *in vitro* enzyme activity for phenytoin or reference drug, and *in vitro* enzyme functional activity (protein stability or enzyme activity with another drug) studies.

Frequency of *CYP2C9*2* (rs1799853) and **3* (rs1057910) Alleles

*CYP2C9*2* and **3* allele frequencies for different populations were obtained from two different sources (see Supplemental Table S5 [see the "Availability of Companion Documents" field]), the first one is Phase 1 results of 1000 Genome Project that contain frequency information for 14 different populations and the other source is subjects in the International Warfarin Pharmacogenetic Consortium that contain three major continental populations. Haplotype and diplotype frequencies for *CYP2C9*2* and **3* alleles were calculated using genotypes from the 1000 Genome Project and calculated diplotype frequencies are presented in Supplemental Tables S6 and S7.

Literature Review for *HLA-B*15:02* Allele Frequency

A table of frequencies of the *HLA-B*15:02* allele in different ethnic populations around the world was assembled from several sources. Frequencies were included from the Allele Frequencies in Worldwide Populations Web site (http://www.allelefrequencies.net/) which lists frequency data for *HLA-B*15:02* from 100 different samples and populations. Where possible, the original paper from which the allele frequencies were obtained was reviewed for the inclusion criteria listed below. Allele frequencies were also obtained by

conducting a search of the PubMed database (1966 to June 2012) and Ovid MEDLINE (1950 to June 2012) using the following criteria: ([HLA or HLA-B or *HLA-B*15:02*] AND [genotype or allele or frequency]) with filter limits set to retrieve "full-text" and "English" literature. Studies from both sources were considered for inclusion if 1) the ethnicity of the population was clearly indicated; 2) either allele frequencies or alleles for *HLA-B* genotypes were reported; 3) the method by which *HLA-B* was genotyped was reliable and proven; 4) the sample population consisted of at least 50 individuals; 5) the study represented publication of novel data, not literature reviews or meta-analyses of previously published data; and 6) the population studied did not have a concomitant disease (such as an autoimmune condition) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of ethnically-diverse individuals were reported without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 271 Africans, 371 non-Caucasian Americans, 14,397 East Asians, 30,640 Europeans including Caucasians worldwide, 491 Middle Easterners, 201 Oceanians, and 235 South or Central Asians (Supplemental Tables S3 and S5 [see the "Availability of Companion Documents" field]).

Number of Source Documents

Using the specified search criteria, 5,193 publications were identified. Following application of the inclusion criteria, 39 publications were reviewed and included in the evidence table.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's (CPIC's) dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include *in vivo* clinical outcome for reference drug, *in vivo* pharmacokinetics/pharmacodynamics for reference drug, *in vitro* enzyme activity for reference drug, and *in vitro* enzyme functional activity (protein stability or enzyme activity with another drug) only.

The evidence summarized in Supplemental Tables S8 and S9 (see the "Availability of Companion Documents" field) was graded using a scaled modified slightly from Valdes et al. (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. The authors chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

Analyses of cost-effectiveness are out of scope for this guideline.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The potential benefit for patients with existing cytochrome P450 (CYP)2C9 (*CYP2C9*) and/or *human leukocyte antigen (HLA)-B*15:02* genotyping information is in avoiding adverse effects in those patients who are CYP2C9 poor metabolizers by making significant reductions in their starting maintenance dose or by selecting alternative agents for those who are *HLA-B*15:02* carriers.

Potential Harms

- For *human leukocyte antigen (HLA)-B*15:02* carriers, a potential risk is that phenytoin therapy may have been needlessly avoided in patients who may not have developed Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN); however, this risk is mitigated because alternatives to phenytoin with comparable effectiveness exist. Another potential risk would be an error in genotyping. Furthermore,

many commercially available genotyping tests do not detect alleles that are rare or *de novo* variants. Other alleles are not well characterized, resulting in uncertainty when predicting the phenotype for some genetic test results. Due to the fact that the absence of *HLA-B*15:02* does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN or in the event of a rare variant that is not detected by the genetic test, a high-risk patient could be prescribed phenytoin or prescribed a higher dose than needed. Moreover, because not all phenytoin-induced adverse events are attributable to *HLA-B*15:02* or CYP2C9 metabolizer status, clinicians should carefully monitor all patients according to standard practices.

- Acute dose-related side effects of phenytoin include sedation, ataxia, dizziness, nystagmus, nausea, and cognitive impairment. The drug is highly allergenic, and rashes ranging from mild eruptions to life-threatening hypersensitivity reactions may be seen. *HLA-B*15:02* is associated with phenytoin-induced SJS and TEN. SJS is characterized by epidermal detachment involving up to 10% of body surface area, whereas TEN usually affects more than 30% of the body surface area. Subacutely, hematologic and hepatic toxicity can occur; the latter is probably a hypersensitivity reaction itself, as it is usually accompanied by rash, whereas the former may consist of leukopenia or pancytopenia.

Contraindications

Contraindications

Acute dose-related side effects of phenytoin include sedation, ataxia, dizziness, nystagmus, nausea, and cognitive impairment. The drug is highly allergenic, and rashes ranging from mild eruptions to life-threatening hypersensitivity reactions may be seen. *Human leukocyte antigen (HLB)-B*15:02* is associated with phenytoin-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS is characterized by epidermal detachment involving up to 10% of body surface area, whereas TEN usually affects more than 30% of the body surface area. Subacutely, hematologic and hepatic toxcitiy can occur; the latter is probably a hypersensitivity reaction itself, as it is usually accompanied by rash, whereas the former may consist of leukopenia or pancytopenia.

Qualifying Statements

Qualifying Statements

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, in addition to identifying questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC guidelines, or for any errors or omissions.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

The application of genotype-based dosing is most appropriate when initiating phenytoin therapy. Obtaining genetic information after months of drug therapy is less helpful, given that the drug dose may have already been adjusted based on plasma concentrations, response, or side effects. As with all diagnostic tests, genetic tests constitute only one of several pieces of clinical information that should be considered before initiating drug therapy.

Implementation of the Guideline

Description of Implementation Strategy

The Supplementary Material online (see the "Availability of Companion Documents" field) contains example clinical decision support (CDS) tools that can be used within electronic health records (EHRs) which assist clinicians to use genetic information to optimize drug therapy. Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems

(Supplementary Tables S10 and S11 online), workflow diagrams (Supplementary Figures S3 and S4 online), tables that translate genotype test results into an interpreted phenotype (Supplementary Table S12 online), and example text for documentation in the EHR and point-of care alerts (Supplementary Tables S13 and S14 online).

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014 Nov;96(5):542-8. [36 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Nov

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

T.E. Klein is a consultant for Personalis. The other authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables, methodological information, and implementation resources, is available from the Pharmacogenomics Knowledgebase Web site .
- A phenytoin translation table is also available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 2, 2015. The information was verified by the guideline developer on August 6, 2015.

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